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HIGH SCHOOL FOOTBALL AND COGNITION LATER IN LIFE

Reports of chronic traumatic encephalopathy (CTE) among professional athletes have raised concerns about those engaged in American high school football. This study explored the long-term association of high school football with cognitive impairment and depression.

In 1957, the Wisconsin Longitudinal Study sampled 10,317 high school graduates, with observations continuing since then. Data concerning participation in football were recorded using high school yearbooks. Data were collected for a total of 2,692 men, of whom 31% played football. The primary outcomes measured at 65 years of age were depression, as measured by the Centers for Epidemiologic Studies Depression Scale (CES-D), and cognition, as measured by combining scores from the Letter Fluency and Delayed Word Recall Tests. Secondary outcomes were cognition at 72 years of age and modified CES-D scores at 54 and 72 years of age.

Compared with the control groups, football players' composite cognitive scores did not significantly differ ($p=0.37$). No significant difference was noted comparing participants of football and non-collision sport controls. The football players had better CES-D depression scores than did the controls ($p=0.01$). This difference was noted at both 54 and 72 years of age.

Conclusion: This study of men graduating from Wisconsin high schools in 1957 found that playing high school football was not adversely associated with cognitive impairment or depression later in life.

Deshpande, S., et al. Association of Playing High School Football with Cognition and Mental Health Later in

Life. *JAMA Neurol.* 2017, Aug.74 (8): 909-918.

MODAFINIL FOR PROLONGED DISORDER OF CONSCIOUSNESS

Modafinil is a central nervous system stimulant commonly used for the treatment of neurologic fatigue in patients with multiple sclerosis. This study assessed the effectiveness of this medication in patients with prolonged disorders of consciousness (PDOC).

Subjects were 26 patients with PDOC with a mean time since injury of 23.17 months. All were administered modafinil up to 400 mg per day, divided by twice daily administrations. The patients were assessed with the Wessex Head Injury Matrix (WHIM). Each participant received at least four assessments before, and four assessments after the administration of modafinil.

At follow-up, the average WHIM scores showed significant improvement ($p=0.002$). Higher WHIM scores were noted in 92% of patient with traumatic brain injury, as compared with 50% of those with nontraumatic brain injury, although this finding did not reach statistical significance.

Conclusion: This retrospective study of patients with brain injury and a prolonged disorder of consciousness found that modafinil may promote an increase in level of consciousness, and may be more effective in those with traumatic as compared to nontraumatic brain injury.

Dhamapurkar, S., et al. Does Modafinil Improve the Level of Consciousness for People with a Prolonged Disorder of Consciousness? Retrospective Pilot Study. *Disabil Rehab.* 2017; 39(26): 2633-2639.

VAGUS NERVE STIMULATION AND LEVEL OF CONSCIOUSNESS

Studies have suggested that patients in a vegetative state have disconnections in long-range cortico-cortical and thalamo-cortical pathways. The neural signature of spontaneous recovery is linked to an increase in thalamo-cortical activity and improved fronto-parietal functional connectivity. This study evaluated the effect of thalamo-cortical stimulation through vagus nerve stimulation in a patient in a vegetative state.

This case study included a 35-year-old male with a history of traumatic brain injury, who had been in a persistent vegetative state for 15 years. Baseline evaluations included behavioral, electroencephalographic, and 18F-FDG PET recordings. The patient then underwent the surgical implant of a vagus nerve stimulator, with stimulation increased to a maximum intensity of 1.5 mA. The effects were monitored for 6 months.

At one month, the patient demonstrated reproducible and consistent improvements in general arousal, sustained attention, body motility and visual pursuit. Scores on the Coma Recovery Scale-Revised test (CRS-R) improved, with the greatest improvement in the visual domain. The change in these scores suggested an improvement from vegetative state to minimally conscious state. The EEG data revealed a significant increase in theta band power ($p<0.0001$), distributed over the occipito-parietal, inferior temporal and fronto-central regions. As an index of consciousness, a weighted symbolic mutual information (wSMI) was calculated, demonstrating that this increase correlated with CRS-R scores of clinical improvement ($p=0.0015$). The PET data revealed increases activity in the occipital-parietal-frontal, and basal ganglion

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regions as early as three months after surgery.

Conclusion: This case study of a patient 15 years in a vegetative state found that a surgically implanted vagal nerve stimulator could improve his cognitive state to a minimally conscious state.

Corazzol, M., et al. Restoring Consciousness with Vagus Nerve Stimulation. *Curr Biol.* 2017, September 25;18: R994-R996.

SYSTOLIC AND PULSE PRESSURE VERSUS OSTEOARTHRITIS OF THE KNEE

Osteoarthritis (OA) is the most common form of arthritis, with at least 30 million adults in the United States diagnosed with clinical OA. Previous studies have suggested an association between metabolic syndrome factors and incident OA. This longitudinal study, nested within the Osteoarthritis Initiative (OAI), explored the association between blood pressure and incident OA.

Eligible subjects were participants of the OAI with no OA at baseline. Blood pressure was measured at baseline, and at 12 and 36 months' follow-up, with pulse pressure (PP) calculated as systolic blood pressure (SBP) minus diastolic blood pressure (DBP). Data were also recorded for physical activity, medication use, and knee radiographs. Radiographic OA (ROA) was defined as a Kellgren and Lawrence grade of two or higher. Covariates included gender, age and body mass index (BMI).

Data were available for 1,930 participants with a mean age of 59.2 years and mean BMI of 27.2 kg/m². A significant increase in the annual rates of ROA was noted with increased SBP and PP quartiles. This was not true of DBP. This association persisted after adjusting for age, gender, BMI and medication use.

Conclusion: This study found that higher systolic blood pressure and pulse pressure, but not diastolic blood pressure, are associated with an increased risk of osteoarthritis of the knee.

Lo, G et al. Systolic and Pulse Pressure Associated with Incident Knee Osteoarthritis: Data from the Osteoarthritis Initiative. *Clin Rheum.* 2017, September; 36(9): 2121-2128.

CHONDROITIN VERSUS CELECOXIB FOR KNEE OSTEOARTHRITIS

For symptomatic osteoarthritis (OA) of the knee, recent guidelines have recommended maintenance therapy with symptomatic slow acting drugs for OA (SYSADOA). As evidence suggests positive benefits of chondroitin sulfate (CS) and crystalline glucosamine sulfate, this study compared the efficacy of a NSAID with CS for OA of the knee.

Subjects were 604 adults over 50 years of age with primary knee OA, randomized to receive daily capsules containing a placebo, CS 800 mg, or Celecoxib 200mg. All were assessed for pain on a 100 mm Visual Analog Scale (VAS), with function measured with the Lequesne Index (LI). Secondary endpoints included the proportion of patients reaching Minimal Clinically Important Improvement (MCII), as well as scores on the Patient Acceptable Symptom State (PASS).

Improvements in VAS pain scores were noted in all three groups as compared with baseline, with the CS and celecoxib groups demonstrating greater reductions than the placebo group (p=0.001 and p=0.009 after six months). No significant difference was found between the CS and celecoxib groups. The LI scores were also significantly improved as compared with placebo, with improvement noted at day 30 in the celecoxib group, but not until day 90 in the CS group. At six months, a greater (though statistically insignificant) proportion of patients reached MCII in the CS and celecoxib groups than in the placebo group.

Conclusion: This study of patients with osteoarthritis of the knee found that 800 mg per day of chondroitin sulfate is similar to 200mg per day of celecoxib for reducing pain and improving function.

Reginster, J., et al. Pharmaceutical-Grade Chondroitin Sulfate is as effective as Celecoxib, and Superior to Placebo, in Symptomatic Knee Osteoarthritis: The Chondroitin versus Celecoxib versus Placebo Trial (CONCEPT). *Ann Rheum Dis.* 2017. DOI: 10.1136/annrheumdis-2016-210860.

PREOPERATIVE OBESITY AND OUTCOME OF LUMBAR DISC SURGERY

Obesity has been implicated as an important factor in the clinical decision making for patients with lumbar intervertebral herniation. During surgery, obese patients present specific technical challenges, and have an increased risk of perioperative complications, including wound infection, blood loss and increased hospital stay. This prospective study explored the functional outcomes of obese patients after lumbar disc surgery.

This prospective study included adults with isolated radicular symptoms secondary to lumbar disc herniation. Body mass index (BMI) was calculated prior to open lumbar microdiscectomy. Outcome measures included a visual analog score to assess the severity of symptoms, the Rowland Morris Disability Questionnaire and the SF-36 Health Survey. In addition, return to work and return to driving were documented. Obesity was defined as a BMI of 30 kg/m² or above.

Of the 107 participants, 34.5% were obese. Prior to surgery, 66.2% of the non-obese and 55.6% of the obese patients were working, with the loss of employment attributed to pain. At three and 12 months, no significant differences were seen between the groups in improvement in back pain, leg pain, paresthesias or numbness. Postoperative quality of life scores improved significantly in both groups at three and 12 months post-surgery, with no significant difference between the two groups ($p=0.119$). At three and 12 months, the groups did not differ significantly in the percentage who returned to work, returned to driving or perceived their surgery as successful.

Conclusion: This prospective study of patients undergoing microscopic lumbar discectomy found that obesity did not significantly impact improvement in quality of life, return to work or improvement in pain.

Brennan, P., et al. Pre-Operative Obesity Does Not Predict Poorer Symptom Control and Quality of Life after Lumbar Disc Surgery. *J Neurosurg.* 2017, September; 7(6): 1-6. <http://dx.doi.org/10.1080/02688697.2017.1354122>.

DULOXETINE REDUCES OPIOID USE AFTER SPINE SURGERY

Multimodal analgesia is the main strategy used for post-operative pain management, with opioids thought to remain necessary to treat moderate to severe pain. Selective serotonin and norepinephrine reuptake inhibitor antidepressants have been shown to reduce pain in persistent and chronic pain syndromes. This study evaluated the efficacy of duloxetine for reducing the dose of fentanyl needed to treat postoperative pain.

Subjects were patients between 18 and 70 years of age who were scheduled for spine surgery. The patients were randomly allocated into two groups; those treated with a placebo or 60mg of duloxetine one hour before surgery and the following morning. After surgery, pain management included self-administered intravenous fentanyl. The patients received ketorolac every 6 hours for 48 hours post-surgery. The main outcome parameter was total consumption of fentanyl, self-administered at 24 and 48 hours after surgery. Pain scores were recorded at two, six, 12, 24, 36 and 48 hours post-surgery.

Total fentanyl consumption was less in the duloxetine group at 24 ($p<0.001$) and 48 ($p<0.000$) hours. No significant difference in pain scores was noted at any time measured.

Conclusion: This study demonstrates that patients undergoing spine surgery who received duloxetine before and after surgery had a significant reduction in fentanyl consumption in the first 48 hours post-surgery.

Bedin, A., et al. Duloxetine as an Analgesic Reduces Opioid Consumption after Spine Surgery. A Randomized, Double-Blind, Controlled Study. *Clin J Pain.* 2017, October; 33(10): 865-869.

LONG-TERM OPIOID THERAPY AND FUNCTIONAL STATUS

While opioids appeared to be effective for the treatment of non-cancer pain in short durations, the long-term efficacy of these medications is not well understood. Using a longitudinal cohort format,

this study followed patients with polyneuropathy, in order to examine the relationship between the duration of opioid therapy and functional status.

Data were obtained from the Rochester Epidemiology Project database, documenting residents of Olmsted County Minnesota since 1966. The study harvested prescription data from ambulatory practice professionals beginning January 1, 2006. From this database, the duration and dose of opioids was determined. Medical records were reviewed for medical diagnoses, with long-term opioid prescription defined as 90 continuous days or longer.

Data were obtained for 17,327 patients from among whom 2,892 with polyneuropathy were identified. Compared with controls, patients with polyneuropathy were more often prescribed long-term opioids (5.4% versus 18.8%, respectively). Of those with polyneuropathy, 18.8% received long-term opioid therapy. Oxycodone accounted for 45.9% of the prescriptions. Compared with short-term use, long-term opioid use was correlated with female gender ($p<0.001$), and having a medical comorbidity.

Of the long-term prescribers, 69.5% were internal medicine, and 13.2% were family medicine physicians. Pain specialists had been consulted in 26.3% of the long-term use cases. Long term users had greater difficulty with ADLs and function than did those receiving short term opioids. Adverse events were more likely among long-term opioid users.

Conclusion: This study found that polyneuropathy increases the likelihood of long-term opioid use, with long-term use associated with poorer functional status.

Hoffman, E., et al. Association of Long-Term Opioid Therapy with Functional Status, Adverse Outcomes and Mortality among Patients with Polyneuropathy. *JAMA Neurol.* 2017, July; 74(7): 773-779.

ELECTROMAGNETIC TRANSDUCTION FOR LOW BACK PAIN

Studies of pulsed electromagnetic fields, approved by the FDA in 1979 for the treatment of bone fractures

and non-unions, have suggested that this treatment can up-regulate anti-inflammatory factors, and down-regulate pro-inflammatory factors. This study was designed to assess the efficacy of electromagnetic transduction therapy (EMTT) for the treatment of low back pain (LBP).

Subjects included adults presenting with nonspecific LBP, randomized to conventional noninvasive treatment (n=44), or a combination of noninvasive treatment plus EMTT (n=44) for six weeks. The noninvasive treatment included physiotherapy with core stabilization, isometric strengthening and heat plus non-opiate analgesics. The EMTT group received two sessions per week for a total of eight sessions. The primary outcome measure was change of disability as measured by the Oswestry Disability Index (ODI) score and the change in subjective pain as measured by a Visual Analog Scale score (VAS).

The VAS pain score improved at 12 weeks in the control and treatment groups by 48.8% and 64.7% respectively ($p<0.001$). This difference was also significant in favor of the treatment group at six weeks ($p<0.001$). In addition, the ODI scores improved more in the EMTT group as compared to the control group at both six ($p<0.001$) and 12 weeks ($p<0.001$).

Conclusion: This study of patients with low back pain found that electromagnetic transduction therapy may be useful as an adjunct to conventional therapy for reducing pain and disability.

Krath, A et al. Electromagnetic Transduction Therapy in Non-Specific Low Back Pain: A Prospective Randomized Controlled Trial. *J Orthop*. 2017, September; 14 (3):410–415.

CIRRHOSIS AND STROKE

While studies have shown cirrhosis to be associated with extrahepatic hemorrhagic and thrombotic processes, the cerebrovascular complications of cirrhosis are not well understood. This study assessed the association between cirrhosis and various stroke subtypes.

This retrospective cohort study included 1,618,059 Medicare beneficiaries treated between 2008

and 2014. From the records, treatment for cirrhosis or its complications were identified. Additionally, the data were reviewed for hospital admission for any stroke, with secondary outcomes including ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage.

Of the patients reviewed, 15,586 were diagnosed with cirrhosis with an average age of 74.1 years. During a mean follow-up of 4.3 years, 77,268 were hospitalized with stroke. The incidence of stroke was 2.17% among patients with cirrhosis and 1.11% for those without. After adjusting for demographic characteristics, stroke risk factors and comorbidities, patients with cirrhosis experienced a higher risk of any stroke (HR 1.4). This association was higher for intracerebral hemorrhage (1.9) and subarachnoid hemorrhage (2.4) than for ischemic stroke.

Conclusion: This study of elderly patients found that cirrhosis is associated with an increased risk of stroke, particularly hemorrhagic stroke.

Parikh, N et al. Association between Cirrhosis and Stroke in an Internationally Representative Cohort. *JAMA Neurol*. 2017, August; 74 (8):927-932.

HIGH-FREQUENCY THERAPY FOR HEMORRHAGIC STROKE

For patients with acute ischemic stroke, early intensive rehabilitation therapy is recommended by the Veterans Affairs/Department of Defense Clinical Practice Guidelines. This study of patients with acute stroke compared the functional gains of high-frequency, daily rehabilitation with traditional weekday treatment.

This retrospective study included patients with cerebral infarctions (CIs) or intracranial hemorrhages (ICHs), excluding subarachnoid hemorrhages. Given a policy change at the study hospital to increase the frequency of therapy to daily in October 2012, outcomes were compared between the periods before and after this change. The population included 661 patients with CI and 245 with ICH. The primary outcome measure was the Barthel index (BI), with effectiveness calculated as discharge BI minus

admission BI divided by maximum BI minus admission BI.

Among the patients with CI, 166 received standard treatment and 149 received high-frequency intervention. Of those with ICH, 124 underwent standard treatment and 121 high-frequency intervention. A multiple linear regression analysis of factors impacting changes in BI effectiveness revealed that high-frequency therapy was correlated with better BI effectiveness scores in the CI group, but not in the ICH group.

Conclusion: This retrospective study suggests that, during rehabilitation after hemorrhagic stroke, daily therapy is superior to weekday-only therapy for improvements in function.

Nakaxora, T., et al. Effectiveness of Seven-Day versus Weekday-Only Rehabilitation for Stroke Patients in an Acute-Care Hospital: A Retrospective, Cohort Study. *Disabil Rehab*. 2017. doi.org/10.1080/09638288.2017.1367964.

THE IMPACT OF CAROTID ARTERY STENTING ON CEREBRAL PERFUSION

Carotid endarterectomy (CEA) is performed to prevent stroke in patients with high-grade carotid artery stenosis. Carotid artery stenting (CAS) is being investigated as an alternative intervention. This study evaluated the cognitive performance of patients with severe, asymptomatic carotid artery stenosis undergoing CAS.

Subjects were adults, 55 to 80 years of age, undergoing CAS for asymptomatic, unilateral, internal carotid artery stenosis of more than 70%. All subjects underwent cognitive assessment, as well as brain imaging, including pulsed arterial spin labeling (pASL), amplitude of low frequency fluctuation (ALFF) and resting state functional MRI (R-fMRI).

Between baseline and 3 months post-surgery, significant improvements were noted in the Mini-Mental State Exam, Verbal Memory Test, and Delayed Recall. An increase in cerebral blood flow, mainly in the left frontal gyrus, anterior cingulate, left occipital gyrus and left cerebellum was noted after surgery. No significant differences

were found between changes in imaging and cognitive assessment.

Conclusion: This study of patients with asymptomatic carotid stenosis found that carotid artery stenting can improve cognition, as well as cerebral perfusion

Sun, T., et al. The Impact of Carotid Artery Stenting on Cerebral Perfusion, Functional Connectivity, and Cognition in Severe Asymptomatic Carotid Stenosis Patients. **Front Neurol.** 2017 Aug 9; 8:403.

REGIONAL DIFFERENCES IN QUALITY OF STROKE CARE

Previous research has demonstrated regional variation in the quality of healthcare in the United States, including stroke care. This study was designed to assess the quality gaps in stroke care, including alteplase (rt-PA) administration and to quantify the extent of gaps in access to neurologic services.

Data were obtained from the Centers for Medicare and Medicaid Services and the U.S. Department of Agriculture Rural-Urban Continuum. From these data, reporting hospitals were categorized as large metropolitan, medium metropolitan, small metropolitan or non-metropolitan. Access to neurologic services was determined for each geographic area, and then compared to that area's population. The average performance levels for each geographic designation on eight stroke measures were compared.

The data from 2013 to 2014 discharges revealed that the worst performance occurred in non-metropolitan hospitals on all stroke measures. The greatest difference was in the use of rt-PA, which occurred in 82.72% of the large, 77.23% of the medium, 68.3% of the small and 52.17% of the non-metropolitan hospitals. Those cared for in certified stroke centers were found to have better quality of care than those in hospitals which were not certified.

Conclusion: This study found a gap in quality of stroke care between metropolitan and nonmetropolitan areas, due in part to the difference in available hospitals with stroke certification, as well as access to neurologic services.

Seabury, S., et al. Regional Disparities in the Quality of Stroke Care. **Am J Emerg Med.** 2017, September; 35: 1234-1239.

BEETROOT JUICE AND MUSCLE FORCE

A growing body of research has demonstrated diverse biological effects of supplementation with dietary inorganic nitrate (NO_3). These results include decreases in VO_2 consumption during exercise. This *in vivo* study examined the effects of nitrite supplementation in the form of beetroot juice (BRJ) on muscle contractile characteristics and muscle function.

Subjects were eight, healthy, recreationally active males who underwent transcutaneous electrical muscle stimulation (TEMS), at low and high frequency, to assess skeletal muscle contractile characteristics before and after intervention. In addition, all participants underwent a muscle biopsy. After baseline assessment, the subjects underwent BRJ supplementation twice daily for a total intake of 26 mmol of NO_3 . On day seven, each consumed BRJ 90 minutes before repeating either the TEMS protocol or undergoing muscle biopsy.

At high frequency stimulation (100 Hz), neither MVC nor peak force produced during induced contractions were altered. In a post hoc analysis, there was no difference in force production from 20-100 Hz while at 10 Hz there was a significant increase in force after supplementation ($p < 0.05$). In addition, the rates of force development and relaxation were increased after supplementation ($p < 0.05$).

Conclusion: This *in vivo* study found that seven days of supplementation with beetroot juice can increase human skeletal muscle force production at low frequency stimulation, as well as the rates of force development and relaxation during evoked twitches.

Whitfield, J., et al. Beetroot Juice Increases Human Muscle Force, without Changing Ca^{2+} -Handling Proteins. **Med Sci Sports Exerc.** 2017, October; 49(10): 2016-2024.

ELECTRONIC CIGARETTE USE AND SMOKING CESSATION

Legislation concerning electronic cigarette (e-cigarette) use varies throughout the world. This study examined the relationship between e-cigarette use and smoking cessation in the U.S. population.

Data for this study were obtained from the U.S. Current Population Survey-Tobacco Use Supplement, a periodic survey administered by the United States Census. From these data, information was obtained concerning the prevalence of e-cigarette, cigarette smoking and cessation. The history and current status of smoking and e-cigarette use were compared.

Of the 161,054 respondents, 8.5% had "ever" used e-cigarettes, while 2.4% were "current users". Former smokers were more likely than current smokers to be daily users of e-cigarettes, with recent quitters found to be the highest proportion at 72.7%. The e-cigarette users were more likely than nonusers to attempt to quit smoking, and also more likely to succeed.

Conclusion: This study found a substantial increase in electronic cigarette use in long-term adult smokers in the United States, with this increase significantly associated with smoking cessation.

Zha, S., et al. E-Cigarette Use and Associated Changes in Population Smoking Cessation: Evidence from U.S. Current Population Surveys. **BMJ.** 2017; 358: J 3262.

VITAMIN D AND RHEUMATOID ARTHRITIS

Vitamin D, a pro-hormone, is thought to play a potential immune-suppressive role, and to exert endocrine action on the immune system cells, generating anti-inflammatory and immunomodulatory effects. This study was designed to better understand the relationship between vitamin D and rheumatoid arthritis (RA).

The study was a *post hoc* analysis of data collected for the Comorbidities in Rheumatoid Arthritis (COMORA) study, an observational, cross-sectional, multicenter, international study of adults with RA. Data were collected for 1,413 patients from 15 countries. Demographic

characteristics and disease specific variables were reported, including drug use and vitamin D supplementation. Disease activity was evaluated by DAS28 scores, characterized as high, moderate, low or in remission. In addition, functional impact of the disease was evaluated by the Health Assessment Questionnaire (HAQ). Current vitamin D levels were collected, and characterized as normal if Vitamin D levels were 30 ng/mL or more, insufficient if 10 to 30 ng/mL and deficient if <10 ng/mL.

The status of vitamin D levels was normal in 36.9%, insufficient in 54.6% and deficient in 8.5% of the subjects. Normal vitamin D status was found in over 50% of patients only in the United States and Italy, and in zero percent of those in Egypt, the Netherlands and the United Kingdom. Vitamin D levels were inversely correlated with DAS28 scores (<0.001).

Conclusion: This multi-national study of patients with rheumatoid arthritis found an inverse association between disease activity and vitamin D levels.

Hajjaj-Hassouni, N., et al. Evaluation of Vitamin D Status and Rheumatoid Arthritis and Its Association with Disease Activity across 15 Countries: "The COMORA Study". *Intern J Rheum.* Volume 2017 (2017), Article ID 5491676, 8 pages. <https://doi.org/10.1155/2017/5491676>

BISPHOSPHONATES FOR TREATING COMPLEX REGIONAL PAIN SYNDROME, TYPE I

Complex regional pain syndrome type I (CPRS-I) is characterized by pain, swelling, vasomotor disorders and skin changes, for which therapeutic management remains challenging. While several trials have demonstrated the analgesic efficacy of bisphosphates in these patients, the authors suggest that early trials were of poor quality. This literature review and meta-analysis was designed to better clarify the efficacy of these medications for the treatment of CPRS-1.

A data search identified randomized, blinded studies of patients diagnosed with CPRS-I. Outcome variables included visual analog scale scores for pain, with function assess with a Short Form-36

Health Survey. From the review, four studies were included in the meta-analysis.

From the studies identified, the mean age range of the subjects was 44.6 to 55.2 years, with the mean duration of CPRS ranging from 3.6 to 21.6 months. In studies measuring pain at 30 to 40 days, as well as in those measuring at the second and third month, those taking bisphosphonates had significantly less pain than did the placebo groups ($p<0.001$ for both). No serious side effects were reported.

Conclusion: This meta-analysis found that, among patients treated for complex regional pain syndrome, type I, bisphosphonates appear to assist with pain reduction.

Chevreau, M., et al. Bisphosphonate for Treatment of Complex Regional Pain Syndrome, Type I: A Systematic Literature Review and Meta-Analysis of Randomized, Controlled Trials versus Placebo. *Joint Bone Spine.* 2017, Jul; 84(4): 393-399.

RIVAROXABAN VERSUS WARFARIN AFTER ATRIAL FIBRILLATION RELATED STROKE

Patients with acute ischemic stroke related to atrial fibrillation (a-fib) are at a high risk of recurrent stroke and intracranial hemorrhage. This study compared the efficacy and safety of a non-vitamin K antagonist oral anticoagulant (NOAC), rivaroxaban, with dose adjusted warfarin among patients with mild a-fib related, acute, ischemic stroke.

Subjects were patients with acute ischemic stroke and nonvalvular a-fib. The subjects were randomized to receive rivaroxaban or warfarin, adjusted to an international normalized ratio (INR) of 2-3. The rivaroxaban group received rivaroxaban, 10 mg once daily for the first five days, followed by 20 mg daily. The warfarin group was titrated to an INR of 2-3. At week four, an MRI was performed to assess for new ischemic lesions and new intracranial hemorrhage.

Data from 183 patients were included in the analysis. The primary endpoint occurred in 49.5% of the rivaroxaban group and in 54.5% of the warfarin group ($p=0.45$). A new ischemic stroke was seen in 29.5% of the rivaroxaban group and 35.6% in the warfarin group ($p=0.38$). A new

intracranial hemorrhage was seen in 31.6% of the rivaroxaban group and in 28.7% of the warfarin group ($p=0.68$). While not statistically significant, parenchymal hematoma with mass effect was observed more frequently in the warfarin group, while type I hemorrhagic infarction was more frequent in the rivaroxaban group.

Conclusion: This study of patients with atrial fibrillation related ischemic strokes found that rivaroxaban and warfarin, initiated within five days of stroke, are safe and effective for preventing early clinical stroke recurrence.

Hong, K., et al. Rivaroxaban versus Warfarin Sodium in the Ultra-Early after Atrial Fibrillation-Related Mild Ischemic Stroke. A Randomized Clinical Trial. *JAMA Neurol.* 2017, Sept 11. doi:10.1001/jamaneurol.2017.2161

NEUROLOGICAL COMPLICATIONS OF ANTI-PROGRAMMED DEATH 1 ANTIBODIES

Neurologic complications have been recognized for many cancer interventions, including anti-programmed death 1 antibodies (PD-1), used for the treatment of solid organ tumors. This study was designed to better understand the frequency, phenotypes and severity of complications when using this intervention.

Subjects were identified through the Mayo Cancer Pharmacy Database in Rochester, Minnesota, for patients receiving anti-PD-1 monoclonal antibodies (pembrolizumab or nivolumab). From this list the authors identified those who developed neurologic disorders after treatment, excluding those who developed neurologic symptoms attributable to their disease or other treatments. All subjects were assessed with the modified Rankin Scale score and with electrodiagnostic testing.

Of the 347 patients, 10 were identified with neurological complications related to the treatment (2.9%). Neuromuscular disorders were the most common of the complications, including myopathy (two) and neuropathy (four). In addition, there were single cases of cerebellar ataxia, autoimmune retinopathy, bilateral internuclear

ophthalmoplegia and headache. The complications occurred after a median of 5.5 cycles of the medicine. Nine patients improved, including one spontaneous improvement and eight with immune rescue treatment, most often using high-dose prednisone.

Conclusion: This retrospective study identified neurologic adverse events among 2.9% of patients treated with anti-PD-1 therapy.

Kao, J., et al. Neurological Complications Associated with Anti-Programmed Death 1 (PD-1) Antibodies. **JAMA Neurol.** 2017, Sept 5. doi:10.1001/jamaneurol.2017.1912.

TRANSCRANIAL MAGNETIC STIMULATION TO DISTINGUISH ALZHEIMER DISEASE FROM FRONTOTEMPORAL DEMENTIA

Alzheimer's disease (AD) and frontotemporal dementia (FTD) are the most common neurodegenerative dementias among those 60 years of age or older. The neuropathological hallmark of AD is amyloid deposits, while those of FTD are TDP-43 and tau inclusions. As transcranial magnetic stimulation (TMS) has been shown to assess distinct intracortical circuits in the central nervous system, this study was designed to assess the neurophysiologic parameters using TMS to differentiate ADD from FTD.

Subjects were 80 patients with probable AD and 64 with probable FTD. Neurophysiologic evaluations were performed at the University of Brescia in Rome at the Noninvasive Brain Stimulation Unit, Santa Lucia Foundation. Using a TMS figure-eight coil, the resting motor threshold was determined on the left motor cortex, recorded from the right first dorsal interosseous muscle during full muscle relaxation. Measurements included short-interval intracortical inhibition (SICI) and facilitation (ICF), long-interval intracortical inhibition, short-latency afferent inhibition (SAI), SICI-ICF, long-interval inhibition (LICI) and SAI.

Among patients with AD, significant impairment in the SAI circuitry was noted ($p < 0.001$), with no such impairment noted in patients with FTD. Those with FTD demonstrated impairment in the SICI-ICF ($p < 0.001$). For the SICI-ICF/SAI ratio, the best cutoff score was 0.98, with a sensitivity of 91.8%, a

specificity of 88.6%, a positive predictive value of 86.2% and a negative predictive value of 93.3% for distinguishing FTD from AD.

Conclusion: This study found that transcranial magnetic stimulation, a noninvasive study, may be helpful in distinguishing Alzheimer's disease from frontotemporal dementia.

Benussi, A., et al. Transcranial Magnetic Stimulation Distinguishes Alzheimer's Disease from Frontotemporal Dementia. **Neurol.** 2017, August 15; 89(7): 665-672.

ACUPRESSURE FOR ACUTE MUSCULOSKELETAL INJURIES

As acupressure has been shown to successfully manage pain for a range of conditions, this study investigated whether this intervention could decrease pain and anxiety in patients with acute musculoskeletal injuries.

Athletes presenting to a musculoskeletal sports clinic with acute sports-related injuries were randomized to one of three groups. These included, acupressure, sham acupressure or no acupressure. Subjects were assessed before and after intervention with visual analog scales for "pain intensity" and "anxiety intensity". Those in the acupressure group received acupressure applied to the Large Intestine four acupoint on the dominant hand for three minutes. The sham group received pressure in the same manner but at a nonreactive point located on the palm of the same hand. The control group did not receive any intervention, and rested alongside the investigator for three minutes.

Participants were 79 athletes, with pain intensity decreasing more in the acupressure group than in the other two groups ($p < 0.001$). No significant difference in pain improvement was seen between the sham and control groups. There was no significant difference in any comparison for improvement in anxiety.

Conclusion: This study of athletes with acute injuries found that acupressure can significantly decrease pain during the early response period.

Macznik, A., et al. Does Acupressure Hit the Mark? A Three-Arm, Randomized, Placebo-Controlled Trial of Acupressure for Pain and

Anxiety Relief in Athletes with Acute Musculoskeletal Sports Injuries. **Clin J Sport Med.** 2017, July; 27(4): 338-343.

COLLAGENASE CLOSTRIDIUM HISTOLYTICUM FOR DUPUYTREN DISEASE NODULES

Dupuytren disease is a common fibro-proliferative disease of the palmar fascia. Two collagenase clostridium histolyticum collagenases, in combination (AUX -1 and AUX-2), have been approved for the treatment of adult patients with a palpable cord. This study assessed the efficacy of this combination for the treatment of Dupuytren nodules.

Subjects with palpable palmar Dupuytren nodules were randomized to receive a placebo or collagenase clostridium histolyticum (CCH) at 0.25mg, 0.40mg or 0.60mg. All were instructed to massage the nodule twice a day until week four. The participants were followed at weeks one, four and eight for assessments of the nodule.

At week four, the nodular surface area had decreased more in the treatment groups than in the placebo group for groups with CCH concentrations of 0.40mg ($p < 0.01$) and 0.60mg ($p = 0.0003$), but not 0.25mg ($p = 0.08$). Nodular hardness improved significantly in all treatment groups as compared with controls. The most common adverse events in the treatment group were contusion/bruising, extremity pain and localized swelling. Severe injection site pain was reported by one patient receiving 0.60 mg.

Conclusion: This study of patients with Dupuytren nodules found that a single injection of CCH can improve the size and hardness of palmar nodules.

Costas, B., et al. Efficacy and Safety of Collagenase Clostridium Histolyticum for Dupuytren Disease Nodules: A Randomized, Controlled Trial. **BMC Musculoskel Dis.** 2017; 18: 374.

NEEDLING VERSUS SHOCKWAVE THERAPY FOR CALCIFIC TENDINITIS

Calcific tendinitis of the shoulder can cause pain in the shoulder and upper arm, with decreased function.

(Continued from page 2)

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administration of their usual
dopaminergic medication (On).

Experimental sessions included a
three-meter timed up and go test
(TUG), modified to simulate a home
environment. The trials were
recorded by video, as well as by
using wearable technologies, with
position sensors placed on each shin,
connected by Bluetooth. Algorithms
were designed to detect and classify
FOG episodes in all subjects.

During the sessions, 25 of 28
patients with FOG demonstrated one
episode during testing. The degree
of gait abnormality was found to be
greater among those with FOG than
among those without. Compared to
the clinical assessment, automatic
FOG detection using wearable
devices resulted in a sensitivity of
93.41%, a specificity of 98.51%, a
positive predictive value of 89.55%
and a negative predictive value of
97.31%.

Conclusion: This study found
that wearable technology can be
used to automatically detect episodes
of freezing of gait in patients with
Parkinson's disease.

Suppa, A., et al. L-Dopa and Freezing
of Gait in Parkinson's Disease:
Objective Assessment through a

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